Official Title of Study:

A PHASE 3B/4 SAFETY TRIAL OF NIVOLUMAB (BMS-936558) IN SUBJECTS WITH ADVANCED OR METASTATIC RENAL CELL CARCINOMA

CHECKMATE 374: CHECKPOINT PATHWAY AND NIVOLUMAB CLINICAL TRIAL EVALUATION 374

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STATISTICAL ANALYSIS PLAN
FOR CLINICAL STUDY REPORT

A PHASE 3B/4 SAFETY TRIAL OF NIVOLUMAB (BMS-936558) IN SUBJECTS WITH ADVANCED OR METASTATIC RENAL CELL CARCINOMA

CHECKMATE 374: CHECKPOINT PATHWAY AND NIVOLUMAB CLINICAL TRIAL EVALUATION 374

PROTOCOL CA209-374

VERSION 2.0

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[redacted]

Research Hypothesis:

The frequency of high grade (CTCAE v4.0 Grade 3-5) IMAEs observed in patients with advanced or metastatic RCC who are treated with nivolumab monotherapy will not differ from historical adverse event data in this patient population.

Schedule of Analyses:

Data cuts for publication purposes will be performed until all subjects have completed the study, which is defined as the time point when the last enrolled subject has had the opportunity for five year for overall survival (OS) follow-up.

The final analysis will be performed when all subjects have completed the study.

2 STUDY DESCRIPTION

2.1 Study Design

This is a Phase 3b/4 safety study of nivolumab monotherapy for the treatment of patients with advanced or metastatic RCC. Approximately 180 subjects will be screened to determine eligibility within 28 days prior to first dose. Approximately 150 eligible subjects will be treated every 2 weeks with 240 mg nivolumab, intravenously over 30 minutes (±5 minutes). Each 28 day dosing period will constitute a cycle.

Subjects will be enrolled into 1 of 3 treatment groups as follows:

- Group 1: Subjects with predominant clear cell histology: 75 subjects (approximate)
- Group 2: Subjects with non-clear cell histology: 50 subjects (approximate, with a minimum of 50 subjects with non-clear cell histology)
- Group 3: Subjects with brain metastases regardless of histology: 25 subjects (approximate).

Note: If enrollment of 25 patients with brain metastases cannot be reached, the number of patients with non-clear cell (preferred) or clear cell histology group will be increased.

Subjects who are found on screening computed tomography (CT)/ magnetic resonance imaging (MRI) to have brain metastases will be enrolled to Group 3, if they do not require active treatment (radiation treatment/corticosteroids). Subjects who are found on screening CT/MRI to

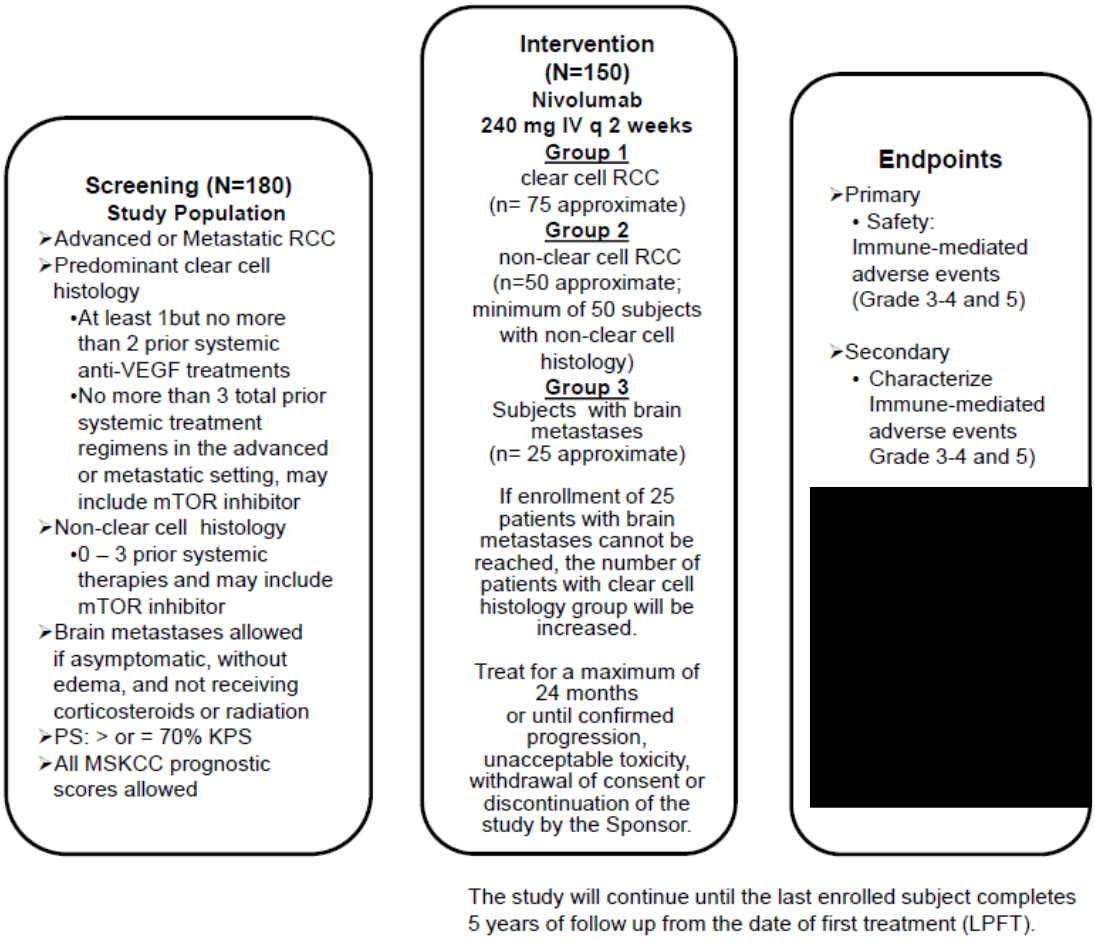
have brain metastases that require immediate treatment with radiation treatment/corticosteroids will be re-enrolled to Group 3 after completing active treatment. Subjects who develop brain metastases while on treatment with nivolumab will not be re-assigned to Group 3 but will remain in the group assigned at enrollment

After screening and enrollment, subjects will be treated for a maximum of 24 months or until confirmed progression, unacceptable toxicity, withdrawal of consent, or the study is discontinued by the sponsor. Study treatment can continue beyond initial investigator assessed progression. The study will close after the last enrolled subject completes 5 years of follow up from the date of first treatment.

Subjects treated in the study who continue to derive benefit from the study treatment after 24 months of treatment or subjects who have not completed 24 months of treatment at discontinuation of the study by the Sponsor, should continue to be treated according to standard of care following completion of the study.

The study design schematic is presented in Figure 1.

Figure 1: Study Design Schematic



2.2 Treatment Assignment

After the subject's eligibility is established and informed consent has been obtained, the subject will be enrolled and a number will be assigned through an interactive voice response system (IVRS). Since this is a single arm study, all enrolled subjects who meet eligibility criteria will be treated with nivolumab at 240 mg IV every 2 weeks.

2.3 Blinding and Unblinding

Not applicable.

2.4 Protocol Amendments

This SAP incorporates the following protocol amendments.

Table 2: Protocol Amendments

Amendments	Date of Issue	Summary of Major Changes
Global Amendment 02	30-Apr-2016	• Eligibility changes: ♦ Patients with previous treatment with mTOR inhibitor for clear-cell RCC histology are now eligible ♦ Patients with non-clear cell histology with up to 3 rather than 2 prior systemic treatments are now eligible ♦ Patients with non-clear cell RCC histology will now include collecting duct and medullary RCC (Appendix 4 updated). • New protocol section (Section 5.6.2) for additional research that may be conducted on specimens already collected from subjects added.
Global Amendment 01	02-Oct-2015	• The title of the study has been revised to reflect changes in the study population. • The term immune-mediated adverse events (IMAEs), replaces the term select adverse events for consistency with nivolumab program. • Total enrollment has been changed to 150 subjects from 250 subjects, with a maximum enrollment of 75 subjects with predominant clear cell histology and approximate enrollments of 50 subjects for non-clear cell and 25 subjects with brain metastases (either histology). • Prior systemic treatments for subjects with non-clear cell histology may include treatment with mechanistic target of rapamycin (mTOR) inhibitor. Subjects with non-clear cell histology who otherwise qualify are eligible with no prior systemic treatment. • Immune-related Response Criteria (irRC) has been removed from the protocol and is no longer an assessment of efficacy. • [redacted] • Nivolumab will be administered to all enrolled

Table 2: Protocol Amendments

Amendments	Date of Issue	Summary of Major Changes
		subjects at a dose level of 240 mg IV every 2 weeks, replacing 3 mg/kg IV every 2 weeks as the dose for all enrolled subjects. • The steroid treatment and taper for brain edema is now specified in protocol Section 3.4.3, Permitted Therapies. • The FACT-G assessment tool will not be administered in this study. • Papillary Renal Cell Carcinoma subtype is specified in protocol Appendix 4. • Appendices of the original protocol have been renumbered to reflect the deletion of irRC (Appendix 2 in original protocol) and the addition [redacted]

3 OBJECTIVES

3.1 Primary

To assess the incidence of high grade (CTCAE v4.0 Grade 3-4 and Grade 5) IMAEs in subjects with advanced or metastatic RCC who are treated with nivolumab monotherapy**.**

3.2 Secondary

To characterize the outcome of all high grade (CTCAE v4.0 Grade 3 4 and Grade 5) IMAEs in subjects with advanced or metastatic RCC who are treated with nivolumab monotherapy.

[redacted]

[redacted]

4 ENDPOINTS

4.1 Primary Endpoint(s)

The primary objective of the study will be assessed by measuring the incidence for high grade (Grade 3-4 and Grade 5) IMAEs.

The IMAEs are the following: skin, endocrinopathy, gastrointestinal, hepatic, renal, pulmonary, and neurologic adverse events.

4.2 Secondary Endpoint(s)

The secondary objective of the study will be assessed by measuring the following:

- median time to onset, median time to resolution of high grade (Grade 3-4 and Grade 5) IMAEs
- percentage of subjects who received immune modulating medication (e.g. corticosteroids, infliximab, cyclophosphamide, Intravenous Immune Globulin [IVIG], and mycophenolate mofetil), or hormonal replacement therapy, the percentage of subjects who received ≥ 40 mg prednisone equivalents, total duration of all immune modulating medications given for the IMAE and summary of subjects with resolution of AEs after initiating these therapies.

[redacted]

[redacted]

5 SAMPLE SIZE AND POWER

Approximately 150 subjects will be treated with nivolumab in this study. This sample size will allow for estimating an incidence rate of 0.67% (n=1 subject with events) with a 95% CI (confidence interval) of (0.02%, 3.7%), or an incidence rate of 2% (n=3 subjects with events)

with a 95% CI of (0.4%, 5.7%). Furthermore, the sample size will allow for enough events to compare incidence with historical adverse event data.

6 STUDY PERIODS, TREATMENT REGIMENS AND POPULATIONS FOR ANALYSES

6.1 Study Periods

6.1.1 Baseline Period

Baseline evaluations or events will be defined as evaluations or events that occur before the date and time of the first dose of study treatment.

In cases where the time (onset time of event or evaluation time and dosing time) is missing or not collected, the following definitions will apply:

- Pre-treatment AEs will be defined as AEs with an onset date prior to but not including the day of the first dose of study treatment
- Baseline evaluations (laboratory tests, pulse oximetry and vital signs) will be defined as evaluations with a date on or prior to the day of first dose of study treatment

If there are multiple valid assessments, the last assessment prior to the first dose of study treatment will be used as the baseline in the analyses. If multiple assessments are collected at the same date (and time if collected), the assessment with the latest database entry date (and time if collected) will considered as baseline.

6.1.2 Post-baseline period

On-treatment AEs will be defined as AEs with an onset date-time on or after the date-time of the first dose of study treatment (or with an onset date on or after the day of first dose of study treatment if time is not collected or is missing). For subjects who are off study treatment, AEs will be counted as on-treatment if the event occurred within 30 days (or 100 days depending on the analysis) of the last dose of study treatment. No "subtracting rule" will be applied when an AE occurs both pre-treatment and post-treatment with the same preferred term and grade.

On-treatment evaluations (laboratory tests, pulse oximetry, and vital signs) will be defined as evaluations taken after the day (and time, if collected and not missing) of first dose of study treatment. For subjects who are off study treatment, evaluations should be within 30 days (or 100 days depending on the analysis) of the last dose of study treatment.

Late emergent drug-related AEs will be defined as drug-related AEs with an onset date greater than 100 days after the last dose of study treatment in subjects off study treatment.

6.2 Treatment Regimens

All subjects will be treated with nivolumab.

6.3 Populations for Analyses

- **All enrolled subjects:** all subjects who signed an informed consent form and were registered into the interactive voice response system (IVRS).

- **All treated subjects:** all subjects who received any dose of nivolumab. This is the primary population for safety and efficacy analyses. Subpopulation analyses will be conducted for subjects in Groups 1-3.
- **All response evaluable subjects:** all treated subjects who have baseline and at least one on-study evaluable tumor measurement.
- **All PD-L1 tested subjects:** all subjects who had a tumor biopsy specimen available for assessment of PD-L1 expression.

7 STATISTICAL ANALYSES

7.1 General Methods

Unless otherwise noted, the bulleted titles in the following subsections describe tabulations of discrete variables, by the frequency and proportion of subjects falling into each category. Percentages given in these tables will be rounded and, therefore, may not always sum to 100%. Continuous variables will be summarized using the mean, standard deviation, median, minimum and maximum values.

Time to event distribution will be estimated using Kaplan Meier techniques. This will be done for endpoints PFS-l, OS and DOR. Median survival time along with 95% CI will be constructed based on a log-log transformed CI for the survivor function S(t)[4,5]. Rates at fixed time points will be derived from the Kaplan Meier estimate and corresponding confidence interval will be derived based on Greenwood formula[6] for variance derivation and on log-log transformation applied on the survivor function S(t)[7].

7.2 Study Conduct

7.2.1 Accrual

The following will be presented on the enrolled population:

- Number of subjects accrued by country and investigational site
- Number of subjects accrued by month.

A by-subject listing of accrual and a by-subject listing of eligibility criteria will be produced.

7.2.2 Relevant Protocol Deviations

The following programmable deviations will be considered as relevant protocol deviations. A table summarize the relevant protocol deviations will be present.

Eligibility:

- Subject having a baseline Karnofsky Performance Status less than 70%.

On-Study:

- Subject not discontinuing study therapy upon evidence of further progression, defined as an additional 20% or greater increase in tumor burden from time of initial progression (including all target lesions and new measurable lesions).

A by subject listing will be produced.

7.3 Study Population

7.3.1 Subject Disposition

The total number of subjects enrolled (treated or not) will be presented along with the reason for not being treated.

Number of subjects who discontinued treatment along with corresponding reason will also be tabulated.

A by-subject listing of pre-treatment subject status and a by-subject listing of end of treatment subject status will be produced.

7.3.2 Demographics and Other Baseline Characteristics

Descriptive statistics will be summarized the following baseline characteristics for all treated subjects.

- Age (descriptive statistics) ; Age (<65, ≥65 and <75, ≥ 75, ≥ 65)
- Gender, Race/Ethnicity, Region
- Karnofsky Performance Status (<70, 70, 80, 90, 100%)
- Height, weight, baseline ECG
- Enrollment Group (1, 2, 3)
- Histology (Clear Cell RCC, Non-Clear Cell RCC)
- Brian metastases (yes/no)
- All lesions: sites of diseases, number of disease sites per subject
- Presence of target lesions, measurement of largest target lesion, sum of reference diameter, site of target lesion, procedures for evaluating target lesion
- Baseline PD-L1 expression
- Baseline MSKCC risk group (Favorable, Intermediate, Poor)

By-subject listings of demographics, ECG, physical measurements, baseline disease characteristics will be provided.

7.3.3 Medical History and Pretreatment Events

Pretreatment events will be summarized by worst CTC grade (grade 1, 2, 3, 4, 5, unknown) by system organ class (SOC)/ preferred term (PT) for all treated subjects.

General medical history will be listed by subject.

7.3.4 Prior Therapy Agents

The following will be summarized:

- Number of prior systemic regimens received in advanced/metastatic setting (0, 1, 2, 3, >3)
- Number of prior systemic regimens with anti-angiogenic agent received in advanced/metastatic setting (0, 1, 2, > 2)
- Prior systemic regimen with cytokine agent in advanced/metastatic setting (yes or no)

- Prior systemic regimen with FDA approved VEGF TKI agent in advanced/metastatic setting (yes or no)
- Prior adjuvant or neo-adjuvant therapy (yes/no)
- Prior surgery related to cancer (yes or no)
- Prior radiotherapy (yes or no)
- Prior systemic therapy classified by therapeutic class and generic name.
- Prior/current other medication classified by anatomic and therapeutic classes.

Medication will be reported using the generic name. Listings of prior systemic cancer therapy, prior radiotherapy and prior surgery related to cancer, prior/current medications by subject will also be provided.

7.3.5 Baseline Examinations

Subjects with abnormal baseline physical examination will be tabulated by examination criteria. A listing of physical examination abnormal findings by subject will also be provided.

7.4 Extent of Exposure

Analyses in this section will be performed in all treated subjects.

7.4.1 Administration of Study Therapy

The following parameters will be summarized (descriptive statistics) by treatment arm:

- Relative dose intensity (%) using the following categories: < 50%; 50 - < 70%; 70 - < 90%; 90 - < 110%; ≥ 110%.
- Number of doses received (summary statistics)
- Cumulative dose
- Duration of treatment: duration of treatment will be presented using a Kaplan-Meier curve whereby the last dose date will be the event date for subjects who discontinued study therapy. Subjects who are still on study therapy will be censored on their last dose date.

A by-subject listing of extent of exposure: weight, number of doses, date of first and last dose, cumulative dose, relative dose intensity, duration of treatment, and reason for discontinuation

Table 3: Administration of study therapy: definition of parameters

	nivolumab
Dosing schedule per protocol	240 mg every 2 weeks
Dose	*Dose (mg)* is defined as Total Dose administered (mg) at each dosing date is collected on the CRF.
Cumulative Dose	*Cum dose (mg) is* sum of the doses (mg) administered to a subject during the treatment period.
Relative dose intensity (%)	*Cum dose (mg) /[(Last dose date - Start dose date + 14) x 240 /14] x 100*
Duration of treatment	*Last dose date - Start dose date +1*

7.4.2 Modifications of Study Therapy

7.4.2.1 Dose Delays

A dose will be considered as actually delayed if the delay is exceeding 2 days (i.e., greater than or equal to 3 days from scheduled dosing date). It is defined as (duration of previous cycle in days - 14). Dose delays will be divided into following categories: 3-7 days, 8-14 days, 15-42 days, >42 days. Reason for dose delay will be retrieved from CRF dosing pages.

The following parameters will be summarized:

- Number of dose delays per subject, Length of Delay and Reason for Dose Delay
- Number of subjects with at least one dose delay along with reason for dose delay.

7.4.2.2 Dose Reductions/Escalations and Infusion Interruption

There will be no dose escalations or reductions of nivolumab allowed. Subjects may be dosed no less than 12 days from the previous dose.

Nivolumab infusion can be interrupted and/or the IV infusion rate can be reduced. This information will be retrieved from CRF dosing pages.

The following will be summarized:

- Number of subjects with at least one infusion with iv rate reduced along with the reason of the rate reduction and number of infusions with IV rate reduction per subject
- Number of subjects with at least one dose infusion interrupted along with the reason for the interruptions and number of infusions interrupted per subject

A by subject listing of study drug administered will be provided. A batch listing number will be also provided.

7.4.3 Concomitant Medications

Concomitant medications, defined as medications other than study medications which are taken at any time on-treatment (i.e. on or after the first day of study therapy and within 100 days following the last dose of study therapy), will be coded using the WHO Drug Dictionary.

The following summary tables will be provided:

- Concomitant medications (subjects with any concomitant medication, subjects by medication class and generic term)
- Immune modulating concomitant medication

A by-subject listing will accompany the tables.

7.5 Efficacy

7.5.1 OS

7.5.1.1 Survival Analysis

The OS curve will be estimated using the Kaplan-Meier (KM) product-limit method, along with the median and its 95% CI using Brookmeyer and Crowley method. Survival rates at different

time points (at 6, 12, 18, 24, and 36 months) will also be estimated using KM estimates from the OS curve. Associated two-sided 95% CIs will be calculated using the Greenwood formula. This analysis will be performed for all treated subjects and all subjects in Groups 1, 2, and 3.

The status of subjects who are censored in the OS Kaplan-Meier analysis will be tabulated for Group 1, 2, and 3, using following categories:

- on-study (on-treatment and not progressed, on-treatment progressed, in follow-up);
- off-study: (lost to follow-up, withdraw consent, etc.).

A by subject listing of overall survival will be produced.

7.5.1.2 Subject Follow-up

The currentness of follow-up for survival will be explored with the following K-M curve. The time between "the last known alive date" and the "Last Patient Last Visit Date" for alive subjects will be presented. Medians along with 95% CI using Brookmeyer and Crowley method will also be provided. The currentness of follow-up will be categorized into the following categories: 0 days, 1-3 months, 3-6 months, 6-9 months, 9-12 months and ≥ 12 months.

7.5.1.3 Follow-up Therapy

Subsequent therapies will be summarized and listed.

- Subsequent Therapy
  - Any subsequent therapy
  - Surgery
  - Radiotherapy
  - Subsequent systemic therapy classified by therapeutic class and generic name
- By Subject Listing of Subsequent Therapy

7.5.1.4 Analysis of Survival by Tumor Response

Survival by response category will be analyzed by treatment group using the landmark method. In the landmark method, a fixed time after the initiation of therapy is selected as a landmark for conducting the analysis of survival by response. Subjects still on study at the landmark time will be separated into two response categories according to whether they have responded before that time. This will assess whether survival from the landmark depends on the subject's response status at the landmark. Subjects who go off protocol (e.g. subjects who die) before the time of landmark will be excluded from the analysis.

The survival curves from Week 8, Month 4, Month 6, Month 8, Month 12, by response status, will be produced using the KM product-limit method for all treated subjects who are still at risk and all subjects in Groups 1, 2, and 3. Two-sided, 95% CIs for median OS will be computed.

[redacted]

7.6 Safety

7.6.1 Primary Analyses

The number and percentage of subjects who report high grade (Grade 3-4 and Grade 5) IMAEs will be summarized for all treated subjects. High grade (Grade 3-4 and Grade 5) IMAEs will be tabulated using worst grade per NCI CTCAE v4.0 criteria by system organ class and Medical Dictionary for Regulatory Affairs (MedDRA) preferred term.

7.6.2 Secondary Analyses

Additional descriptive statistics will include median values using the Kaplan-Meier (KM) product-limit method with 95% CI using Brookmeyer and Crowley of time to onset and time to resolution of IMAEs, and will be presented for all treated subjects in Groups 1, 2, and 3. Time to onset is calculated from first dosing date to the event onset date. If a subject never experienced the given AE, the subject will be censored at the last contact date. Time to resolution is calculated from the AE onset date to AE end date. If an AE is ongoing at the time of analysis, the time to resolution will be censored at the last contact date.

Management of high-grade (CTCAE v4.0 Grade 3-4 and Grade 5) IMAEs will be characterized by measuring percentage of subjects who received immune modulating medication (or hormonal replacement therapy), percentage of subjects who received ≥ 40 mg prednisone equivalents, and total duration of all immune modulating medications given for the event, in all treated subjects who have experience high-grade (CTCAE v4.0 Grade 3-4 and Grade 5) IMAEs and all subjects in Groups 1, 2, and 3.

7.6.3 Deaths

See Section 7.6.1 of Core Safety SAP

7.6.4 Serious Adverse Events

See Section 7.6.2 of Core Safety SAP

7.6.5 Adverse Events Leading to Discontinuation of Study Therapy

See Section 7.6.3 of Core Safety SAP

7.6.6 Adverse Events Leading to Dose Delay of Study Therapy

See Section 7.6.4 of Core Safety SAP

7.6.7 Adverse Events

See Section 7.6.5 of Core Safety SAP

7.6.8 Immune Mediated Adverse Events

IMAEs are specific events occurring within 100 days of the last dose of study drug (which includes pneumonitis, diarrhea/colitis, hepatitis, nephritis/renal dysfunction, rash, and endocrine abnormalities [adrenal insufficiency, hypothyroidism/thyroiditis, hyperthyroidism, diabetes mellitus, and hypophysitis]), regardless of causality, for which subjects received immunosuppressive medication for treatment of the event. The exception to the immunosuppressive medication criteria for IMAEs is endocrine events (hypothyroidism/thyroiditis, hyperthyroidism, hypophysitis, diabetes mellitus, adrenal insufficiency), which are included regardless of treatment since these events are often managed without immunosuppression.

Unless otherwise specified, analyses will be performed by IMAE category on events where immune modulating medication was initiated. Analyses may also be repeated by categories of endocrine events.

7.6.8.1 Incidence of IMAE

IMAEs will be summarized for each category:

- Overall summary of any IMAEs by worst CTC grade presented by Category/PT (any grade, grade 3-4, grade 5)
- Overall summary of any serious IMAEs by worst CTC grade presented by Category /PT (any grade, grade 3-4, grade 5)
- Overall summary of any IMAEs leading to discontinuation by worst CTC grade presented by Category/PT (any grade, grade 3-4, grade 5)
- Overall summary of any IMAEs leading to drug delay by worst CTC grade presented by Category/PT (any grade, grade 3-4, grade 5)
- Overall summary of drug-related IMAEs by worst CTC grade presented by Category/PT (any grade, grade 3-4, grade 5)
- Overall summary of drug-related IMAEs leading to discontinuation by worst CTC grade presented by Category/PT (any grade, grade 3-4, grade 5)
- Overall summary of any IMAEs by worst CTC grade presented by Category/PT (grade 1, 2, 3, 4, 5, unknown)
- Overall summary of any serious IMAEs by worst CTC grade presented by Category/PT (grade 1, 2, 3, 4, 5, unknown)
- Overall summary of any IMAEs leading to discontinuation by worst CTC grade presented by Category/PT (grade 1, 2, 3, 4, 5, unknown)
- Overall summary of any IMAEs leading to drug delay by worst CTC grade presented by Category/PT (grade 1, 2, 3, 4, 5, unknown)

The analyses will be conducted using the 100-day safety window.

By-subject IMAE listing will be provided.

7.6.8.2 Time-to onset of IMAE

Time-to onset of the following specific events will be summarized for each category of IMAEs:

- Time-to onset of any grade IMAE
- Time-to onset of grade 3 to 5 IMAE
- Time-to onset of any grade IMAE where immune modulating medication was initiated
- Time-to onset of grade 3 to 5 IMAE where immune modulating medication was initiated

The following summary statistics will be reported for treated subjects who experienced at least one immune-mediated adverse event from the category: median, min and max. Median time to onset along with 95% confidence interval using the Kaplan-Meier technique is also reported for all treated subjects. If the subject did not experience a IMAE in the category, time-to onset will be censored at the maximum follow-up time of all subjects in their respective treatment group (i.e. for subjects without an event, follow-up time is defined from first dosing date up to last dosing date +100 days if subjects are off treatment and followed for at least 100 days, otherwise it is defined up to the last known alive date).

See time-to onset definition subsection of Appendix 1 for additional details. The analyses will be conducted using the 100-day safety window.

7.6.8.3 Time-to resolution of IMAE

Time to resolution of the following specific events will be summarized separately for each category/subcategory.

- Time-to resolution of any grade IMAE
- Time-to resolution of grade 3 to 5 IMAE

Time-to resolution analyses are restricted to treated subjects who experienced the specific events. Time-to resolution where immune modulating medication was initiated analyses is restricted to treated subjects who experienced the specific events and who received immune modulating medication during the longest IMAE.

The following summary statistics will be reported: percentage of subjects who experienced the specific events, percentage of subjects with resolution of the longest IMAE, median time-to resolution along with 95% CI (derived from Kaplan-Meier estimation) and ranges.

See time-to resolution definition subsection of Appendix 1 for additional details.

The analyses will be conducted using the 100-day safety window.

7.6.8.4 Immune modulating medication for IMAE

For each category of IMAE, the following will be reported for each treatment group:

- Percentage of subjects who received immune modulating concomitant medication for management of other events of special interest in the category among subjects who experienced at least one other events of special interest in the category.
- The total medication treatment duration, duration of high dose of corticosteroid and tapering duration (summary statistics)

These analyses will be performed on any IMAE, grade 3-5 IMAE.

The analysis will be conducted using the 100-day safety window.

7.6.9 Multiple Events

See Section 7.6.8 of Core Safety SAP

7.6.10 Select Adverse Events

Unless otherwise specified, analyses will be performed by select AE category. Some analyses may also be repeated by subcategory of endocrine events.

7.6.10.1 Incidence of select AE

Select AEs will be summarized by treatment group for each category/subcategory:

- Overall summary of any select AEs by worst CTC grade presented by Category or Subcategory/PT (grade 1, 2, 3, 4, 5, unknown)

- Overall summary of any select AEs by worst CTC grade presented by Category or Subcategory/PT (any grade, grade 3-4, grade 5)
- Overall summary of drug-related select AEs by worst CTC grade presented by Category or Subcategory / PT (grade 1, 2, 3, 4, 5, unknown)
- Overall summary of drug-related select AEs by worst CTC grade presented by Category or Subcategory / PT (any grade, grade 3-4, grade 5)
- Overall summary of any serious select AEs by worst CTC grade presented by Category or Subcategory /PT (any grade, grade 3-4, grade 5)
- Overall summary of drug-related serious select AEs by worst CTC grade presented by Category or Subcategory /PT (any grade, grade 3-4, grade 5)
- Overall summary of any select AEs leading to discontinuation by worst CTC grade presented by Category or Subcategory /PT (any grade, grade 3-4, grade 5)
- Overall summary of drug-related select AEs leading to discontinuation by worst CTC grade presented by Category or Subcategory /PT (any grade, grade 3-4, grade 5).

The analyses will be conducted using the 30-day safety window, and some will be repeated using the 100-day safety window.

Summary of frequency of unique select AE by Category will also be reported for each treatment group.

By-subject select AE listing and a select AE definition listing will be provided.

7.6.10.2 Time-to onset of select AE

Time-to onset of the following specific events will be summarized for each category/subcategory of select AEs for treated subjects who experienced at least one select adverse event from the category/subcategory, reporting median, min, and max:

- Time-to onset of any grade select AE by treatment group
- Time-to onset of grade 3 to 5 select AE by treatment group
- Time-to onset of any grade drug-related select AE by treatment group
- Time-to onset of grade 3 to 5 drug-related select AE by treatment group

See time-to onset definition subsection of Appendix 1 for additional details. The analyses will be conducted using the 30-day safety window.

7.6.10.3 Time-to resolution of select AE

Time to resolution of the following specific events will be summarized separately for each category/subcategory.

- Time-to resolution of any grade select AE by treatment group
- Time-to resolution of grade 3 to 5 select AE by treatment group
- Time-to resolution of any grade drug-related select AE by treatment group
- Time-to resolution of grade 3 to 5 drug-related select AE by treatment group

- Time-to resolution of any grade select AE where immune modulating medication was initiated, by treatment group.
- Time-to resolution of grade 3 to 5 select AE where immune modulating medication was initiated, by treatment group.
- Time-to resolution of any grade drug-related select AE where immune modulating medication was initiated, by treatment group
- Time-to resolution of grade 3 to 5 drug-related select AE where immune modulating medication was initiated, by treatment group

Time-to resolution analyses are restricted to treated subjects who experienced the specific events. Time-to resolution where immune modulating medication was initiated analyses are restricted to treated subjects who experienced the specific events and who received immune modulating medication during the longest select AE.

See time-to resolution definition subsection of Appendix 1 for additional details. The analyses will be conducted using the 30-day safety window.

7.6.10.4 Immune Modulating Medication for Select AE

For each category/subcategory of select AEs, the following will be reported for each treatment group:

- Percentage of subjects who received immune modulating concomitant medication for management of any select AE in the category among subjects who experienced at least one select adverse event in the category/subcategory.
- The total medication treatment duration, duration of high dose of corticosteroid and tapering duration (summary statistics)

These analyses will be performed on any select AEs, drug-related select AEs, grade 3-5 select AEs and drug-related select AEs.

The analysis will be conducted using the 30-day safety window.

7.6.11 Other Events of Special Interest

Unless otherwise specified, analyses will be performed by other events of special interest category.

7.6.11.1 Incidence of other events of special interest

Other events of special interest will be summarized by treatment group for each category:

- Overall summary of other events of special interest by worst CTC grade presented by Category/PT (grade 1, 2, 3, 4, 5, unknown)
- Overall summary of other events of special interest by worst CTC grade presented by Category or Subcategory/PT (any grade, grade 3-4, grade 5)
- Overall summary of drug-related other events of special interest by worst CTC grade presented by Category or Subcategory / PT (grade 1, 2, 3, 4, 5, unknown)

- Overall summary of drug-related other events of special interest by worst CTC grade presented by Category or Subcategory / PT (any grade, grade 3-4, grade 5)
- Overall summary of serious other events of special interest by worst CTC grade presented by Category/PT (grade 1, 2, 3, 4, 5, unknown)
- Overall summary of other events of special interest leading to discontinuation by worst CTC grade presented by Category/PT (grade 1, 2, 3, 4, 5, unknown)
- Overall summary of other events of special interest where immune modulating medication was initiated by worst CTC grade presented by Category/PT (grade 1, 2, 3, 4, 5, unknown)
- Overall summary of other events of special interest where immune modulating medication was initiated by worst CTC grade presented by Category/PT (any grade, grade 3-4, grade 5)
- Overall summary of drug-related other events of special interest where immune modulating medication was initiated by worst CTC grade presented by Category/PT (grade 1, 2, 3, 4, 5, unknown)

The analyses will be conducted using the 30-day safety window, and repeated using the 100-day safety window.

7.6.11.2 Time-to onset of other events of special interest

Time-to onset of the following specific events will be summarized for each category of other events of special interest for treated subjects who experienced at least one event from the category, reporting median, min, and max:

- Time-to onset of any grade other events of special interest by treatment group
- Time-to onset of grade 3 to 5 other events of special interest by treatment group
- Time-to onset of any grade drug-related other events of special interest by treatment group
- Time-to onset of grade 3 to 5 drug-related other events of special interest by treatment group
- Time-to onset of any grade other events of special interest where immune modulating medication was initiated, by treatment group.
- Time-to onset of grade 3 to 5 other events of special interest where immune modulating medication was initiated, by treatment group.

See time-to onset definition subsection of Appendix 1 for additional details. The analyses will be conducted using the 30-day safety window, and some will be repeated using the 100-day safety window.

7.6.11.3 Time-to resolution of other events of special interest

Time to resolution of the following specific events will be summarized separately for each category.

- Time-to resolution of any grade other events of special interest by treatment group
- Time-to resolution of grade 3 to 5 other events of special interest by treatment group
- Time-to resolution of any grade drug-related other events of special interest by treatment group

- Time-to resolution of grade 3 to 5 drug-related other events of special interest by treatment group
- Time-to resolution of any grade other events of special interest where immune modulating medication was initiated, by treatment group.
- Time-to resolution of grade 3 to 5 other events of special interest where immune modulating medication was initiated, by treatment group.

Time-to resolution analyses are restricted to treated subjects who experienced the specific events. The analyses will be conducted using the 30-day safety window, and some will be repeated using the 100-day safety window.

See time-to resolution definition subsection of Appendix 1 for additional details.

7.6.11.4 Immune Modulating Medication for other events of special interest

For each category of other events of special interest, the following will be reported for each treatment group:

- Percentage of subjects who received immune modulating concomitant medication for management of other events of special interest in the category among subjects who experienced at least one other events of special interest in the category.
- The total medication treatment duration, duration of high dose of corticosteroid and tapering duration (summary statistics)

These analyses will be performed on any other events of special interest, grade 3-5 other events of special interest.

The analysis will be conducted using the 100-day safety window.

7.6.12 Laboratory Parameters

7.6.12.1 Hematology

See Section 7.6.9.1 of Core Safety SAP

7.6.12.2 Serum Chemistry

See Section 7.6.9.2 of Core Safety SAP

7.6.12.3 Electrolytes

See Section 7.6.9.3 of Core Safety SAP

7.6.12.4 Additional Analyses

See Section 7.6.9.4 of Core Safety SAP

7.6.13 Vital Signs and Pulse Oximetry

See Section 7.6.10 of Core Safety SAP

7.6.14 Immunogenicity Analyses

Not applicable

7.6.15 Pregnancy

See Section 7.6.12 of Core Safety SAP

7.6.16 Clinical Safety Program (CSP)

Not applicable

7.6.17 Adverse Events By Subgroup

See Section 7.6.14 of Core Safety SAP

- [redacted]

7.8 Outcomes Research Analyses

Descriptive summary statistics of Patient Reported Outcomes will be presented at baseline and each on-study time point, unless otherwise specified. Mean changes from baseline for each of the 2 scales will be calculated for each subject at each on-study time point. In addition, subject compliance will be described per time point by the proportion of subjects who filled out the QoL assessments over the numbers of subject known to be alive and eligible for assessment at these time points. The analysis will be performed for all treated subjects and in Groups 1, 2, and 3.

[redacted]

[redacted]

[redacted]

7.9 Health Care Resource Utilization

Hospitalization rate based on person year will be summarized in table. Descriptive summary statistics of length of stay will be presented at baseline and each on-study time point, unless otherwise specified. The analysis will be performed for all treated subjects and in Groups 1, 2, and 3.

All hospitalization will be presented in a listing.

8 CONVENTIONS

The following conventions may be used for imputing partial dates for analyses requiring dates:

For missing and partial adverse event onset dates, imputation will be performed using the Adverse Event Domain Requirements Specification[1]. Missing and partial Non-Study Medication Domain dates will be imputed using the derivation algorithm described in BMS Non-Study Medication Domain Requirements Specification[2].

For death dates, the following conventions will be used for imputing partial dates:

- If only the day of the month is missing, the 1st of the month will be used to replace the missing day. The imputed date will be compared to the last known alive date +1 day and the maximum will be considered as the death date.
- If the month or the year is missing, the death date will be imputed as the last known alive date + 1 day
- If the date is completely missing but the reason for death is present the death date will be imputed as the last known alive date + 1 day

For date of progression, the following conventions will be used for imputing partial dates:

- If only the day of the month is missing, the 1st of the month will be used to replace the missing day.

- If the day and month are missing or a date is completely missing, it will be considered as missing.

* In case, the date of death is present and complete, the imputed progression date will be compared to the date of death. The minimum of the imputed progression date and date of death will be considered as the date of progression.

The following conversion factors will be used to convert days to months or years: 1 month = 30.4375 days and 1 year = 365.25 days.

Duration (e.g. time from first diagnosis of NSCLC to first dosing date, duration response, and time to response) will be calculated as follows:

Duration = (Last date - first date + 1)

All statistical analyses will be carried out using SAS (Statistical Analysis System software, SAS Institute, North Carolina, USA) unless otherwise noted.

9 CONTENT OF REPORTS

The complete list of analyses contributing to the clinical study report is given in the Data Presentation Plan.

APPENDIX 1 ADVERSE EVENTS OF INTEREST DEFINITION AND CONVENTIONS

The adverse events of interest including IMAE, select AE, and other event of special interest consist of a list of preferred terms grouped by specific category and by subcategory. These categories and subcategories are defined by the Sponsor and the list that is most current at the time of analysis will be used. Also changes may be made to this list with each new version of MedDRA.

Time-to onset definition

Time-to onset of AE (any grade) for a specific category (e.g. pulmonary events, gastrointestinal events, ...) is defined as the time between the day of the first dose of study treatment and the onset date of the earliest AE (of any grade) in this category.

If the subject did not experience an AE (of any grade) in the category, time-to onset will be censored at the maximum follow-up time of all subjects in their respective treatment group (i.e for subjects without an event, follow-up time is defined from first dosing date up to last dosing date +30 days (or 100 days depending on the analysis) if subjects are off treatment and followed for at least 30 days (or 100 days depending on the analysis) , otherwise it is defined up to the last known alive date). The resulting Kaplan-Meier plot will represent the cumulative rate of the select AE (any grade) in the category over time.

Time-to onset of AE (grade 3-5) for a specific category is defined similarly but restricted to grade 3-5 AEs.

Time-to onset of drug-related (grade 3-5 or any grade) AE for a specific category is defined similarly but restricted to drug-related AEs.

Time-to onset for a specific subcategory is defined similarly but restricted to event of this subcategory.

Time-to resolution definition

In order to derive the time-to resolution, overlapping or contiguous AEs within a specific category will be collapsed into what will be termed “clustered” AEs. For example, if a subject (without pre-treatment AE) experienced an AE from 1st to 5th January, another AE (with different PT but within same category) from 6th to 11th January and same AE from 10th to 12th January, these will be collapsed into one clustered AE from 1st to 12th January. Table 4 is summarizing key derivation steps for each type of clustered AEs.

Time-to resolution of AE (any grade) for a specific category is defined as the longest time from onset to complete resolution or improvement to the grade at baseline among all clustered select AEs in this category experienced by the subject. Events which worsened into grade 5 events (death) or have a resolution date equal to the date of death are considered unresolved. If a clustered AE is considered as unresolved, the resolution date will be censored to the last known date alive. Improvement to the grade at baseline implies that all different adverse events in the clustered adverse event should at least have improved to the corresponding (i.e. with same

preferred term) baseline grade. This measure is defined only for subjects who experienced at least one AE in the specific category.

The time-to resolution of AE (grade 3-5) for a specific category is defined similarly with an onset date corresponding to a grade 3-5 AE.

Time-to resolution of drug-related AE (any grade or grade 3-5) is defined similarly but restricted to drug-related AE.

The time-to resolution of AE (any grade or grade 3-5, drug-related or all) where immune modulating medication was initiated is defined similarly with the additional condition that the subject started an immune modulating medication during the longest AE resolution period.

Time-to resolution for a specific subcategory is defined similarly but restricted to event of this subcategory.

Table 4: Derivation of clustered AE of interest

Type of clustered AE of interest	Derivation
Any grade	Collapse any on-treatment AE from the same category
Drug-related of any grade	Collapse any on-treatment drug-related AE from the same category
Grade 3-5	Collapse any on-treatment AE from the same category. Resolution will be based on the onset date of the earliest grade 3-5 records (if no grade 3-5 record, clustered AE is excluded)
Drug-related of Grade 3-5	Collapse any on-treatment drug-related AE from the same category Resolution will be based on the onset date of the earliest grade 3-5 record (if no Grade 3-5 record, clustered AE is excluded)

The algorithm for collapsing adverse event of interest (IMAE, select AE, other event of special interest) records is using the following conventions:

For each subject and specified category, the corresponding adverse event records will be collapsed when:

1) Multiple adverse event records have the same onset date.
2) The onset date of an event record is either the same day or 1 day later than the resolution date of a preceding event record (contiguous events).

The onset date of an event record is after the onset date and prior to or on the resolution date of a preceding event record (overlapping events).

DOCUMENT HISTORY

Version Number	Date	Author(s)	Description
1.0	13JAN2016	[redacted]	Initial version
2.0	09SEP2016		Modify IMAE section; add select AE and other events of special interest sections; add Appendix 1. Update SAP v1.0 to add more details of the analysis.